REMARKS

Applicants acknowledge receipt of a Non-Final Office Action dated May 23, 2006. In this response Applicants amend claims 1, 2, 4, 6, 10, 13-15, 17-20, 24, 25, 28, 30, 32, 34, 35, 38, 42, 43, 45, 48, 55, and 57. Claims 67-81 are added and claims 3, 8, 9, 11, 12, 16, 21-23, 26, 27, 31, 36, 37, 39-41, and 63 are withdrawn. Following entry of these amendments, claims 1, 2, 4-7, 10, 13-15, 17-20, 24, 25, 28-30, 32-35, 38, 42-62, and 64-81 are pending in the application.

No new matter has been introduced. Support for the amendments to the following claims can be found, e.g., in the following places in the publication of the instant application, U.S. 2005/0058982:

- claim 1 – paragraph [0064] and claim 12 as originally filed;
- claims 2, 15, 17, 30, 76, and 77 – paragraphs [0049] and [0053];
- claims 6, 19, 34, 68, 71, 74, and 79 – paragraph [0042];
- claim 10 – claim 12 as originally filed;
- claims 13, 28, 43, 57, and 81 – paragraph [0064] and the corresponding claims as originally filed;
- claim 14 – paragraphs [0063] and [0064];
- claims 20 and 35 – paragraphs [0053] and [0063];
- claim 24 – paragraphs [0010], [0047], and [0064];
- claim 38 – paragraph [0064] and claim 41 as originally filed;
- claim 55 – paragraphs [0062]-[0064] and [0101] and claim 55 as originally filed; and
- claims 67, 69, 70, 72, 73, 75, 78, and 80 – paragraphs [0041] and [0043].

Support for the amendment to the claims reciting 3'-untranslated region (3'-UTR), NS3 helicase, C1, C2, C3, C4, C5, 5B1, 5B2, 5B3, 5B4, 5B5, 5B6, 5B7, 5B8, 5U8, 5U9, 5U10, or the sequence targeted by siRNA5 as a target sequence can be found, e.g., in Figures 1, 2, and 5, paragraph [0064], and the corresponding claims as originally filed.

The amendments to claims 4, 32, and 42 follow from the withdrawal of claims 3, 31, and 41, respectively. Further, the amendments to claims 25 and 45 follow from the amendments to claims 24 and 43, respectively. Finally, the amendments to claims 18 and 48 are typographical corrections.

Reconsideration of the present application is respectfully requested in view of the foregoing amendments and the remarks which follow.

Rejections under 35 U.S.C. § 112, Second Paragraph

On page 2 of the Office Action, the PTO has rejected claims 2, 3, 24-27, 30, 31, and 45 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The rejections of claims 2, 3, 24-27, 30 and 31 are moot in light of the amendments to the claims. Applicants respectfully submit that a person of ordinary skill in the art (a "skilled artisan") would understand the meaning of the term "corresponds to" in claim 45 (see, e.g., paragraph [0063]).

In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejection of claims 2, 3, 24-27, 30, 31, and 45 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 112, First Paragraph

1. Written Description

Claims 1-66 are rejected on page 3 of the Office Action for allegedly failing to comply with the written description requirement under 35 U.S.C. § 112, first paragraph. The written description requirement may be satisfied by disclosing a representative number of species that are representative of the entire claimed genus or by disclosing feature(s) or attribute(s) common to a substantial number of species in the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997); Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1, "Written Description" Requirement, 66 Fed. R. 1099, 1106 (2001).

Applicants respectfully submit that Applicants have satisfied either criterion of the written description requirement. First, Applicants have disclosed a representative number of RNA molecules that target a hepatitis C virus (HCV) nucleotide sequence selected from the group consisting of 3'-untranslated region (3'-UTR), NS3 helicase, C1, C2, C3, C4, C5, 5B1, 5B2, 5B3, 5B4, 5B5, 5B6, 5B7, 5B8, 5U8, 5U9, 5U10, and the sequence targeted by siRNA5 (see, e.g., Figures 1, 2, 6, 7, 9 and 15, and Examples 1, 2, 4, 6, 7, 9 and 12). Second, the subject matter of all the pending claims shares a "common attribute." All the pending claims relate to RNA molecules that target an HCV nucleotide sequence selected from the group

consisting of 3'-UTR, NS3 helicase, C1, C2, C3, C4, C5, 5B1, 5B2, 5B3, 5B4, 5B5, 5B6, 5B7, 5B8, 5U8, 5U9, 5U10, and the sequence targeted by siRNA5. For either of these two reasons, Applicants have fulfilled the written description requirement.

In view of the foregoing amendments and remarks, Applicants respectfully request the withdrawal of the rejection of claims 1-66 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement.

2. Enablement

The PTO has rejected claims 1-23, 28-42, 45, 46, 54-56, and 64-66 on page 4 of the Office Action for allegedly being non-enabled under 35 U.S.C. § 112, first paragraph. While the PTO acknowledges that the disclosure is "enabling for the in vitro targeting and inhibition of expression of HCV or luciferase using particularly described siRNA molecules," the PTO asserts that *in vitro* efficacy of nucleic acid molecules is generally not predictive of *in vivo* efficacy. Related to *in vivo* efficacy, the PTO raises issues of *in vivo* stability and *in vivo* delivery.

Applicants respectfully submit that the disclosure of the instant applicant, coupled with the knowledge of a skilled artisan, would enable a skilled artisan to practice the claimed inventions. First, Applicants have demonstrated the stability of 2'-modified siRNA molecules in human serum (see, e.g., Fig. 13, paragraph [0024], and Example 10).

Second, nucleic acid molecules have been successfully delivered to their target sites *in vivo* using various methods, including viral vectors, liposomes, and hydrodynamic delivery. For example, electroporation results in the efficient delivery of naked nucleic acid molecules to organs and tissues as diverse as, e.g., muscle, blood vessel wall, and the cornea. See, e.g., L.C. Smith *et al.*, Advances in plasmid gene delivery and expression in skeletal muscle, *Curr. Opin. Mol. Ther.*, 2(2):150-54 (Apr. 2000); J.B. Martin *et al.*, Gene transfer to intact mesenteric arteries by electroporation, *J. Vasc. Res.*, 37(5):372-80 (Sept.-Oct. 2000); K. Blair-Parks *et al.*, High-level gene transfer to the cornea using electroporation, *J. Gene Med.*, 4(1): 92-1000 (Jan.-Feb. 2002). Moreover, the instant application teaches attaching a receptor-binding ligand to an siRNA molecule to direct delivery of the siRNA molecule to a target site *in vivo*, and cites examples of targeted delivery of siRNA molecules using this technique (see, e.g., paragraphs [0054]-[0061]).

Third, efficient *in vivo* delivery of siRNA molecules has resulted in effective and specific *in vivo* suppression of mRNA levels and protein production of targeted viral and non-viral genes. See, e.g., D.L. Lewis *et al.*, Efficient delivery of siRNA for inhibition of gene expression in postnatal mice, *Nat. Genet.*, 32(1):107-08 (Sept. 2002); Q. Ge *et al.*, RNA interference of influenza virus production by directly targeting mRNA for degradation and indirectly inhibiting all viral RNA transcription, *Proc. Natl. Acad. Sci. USA*, 100(5):2718-23 (Mar. 2003); E. Song *et al.*, RNA interference targeting Fas protects mice from fulminant hepatitis, *Nat. Med.*, 9(3):347-51 (Mar. 2003); D.R. Sorensen *et al.*, Gene silencing by systemic delivery of synthetic siRNAs in adult mice, *J. Mol. Biol.*, 327(4):761-76 (Apr. 2003).

Based on the detailed disclosure of the instant application and the above evidence of the stability, efficient delivery, and efficacy of siRNA molecules in specifically inhibiting viral and non-viral gene expression *in vivo*, a skilled artisan would be able to practice the claimed inventions without undue experimentation. Therefore, Applicants respectfully request withdrawal of the rejection of the various claims for non-enablement.

Rejections under 35 U.S.C. §102

On page 9 of the Office Action, the PTO has rejected claims 1-4, 7-11, 14-17, 20-23, 28-32, 35-40, 43, 45-47, 51, 53-57, 62, and 64 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. App. Pub. No. 2003/0153519 to Kay *et al.* ("Kay"). Under § 102, a single prior art reference can anticipate a claim only if it discloses, either expressly or inherently, each and every feature of the claim. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

Applicants respectfully submit that Kay cannot anticipate any of the rejected claims because Kay fails to teach each and every feature of any of these claims. For example, Kay does not teach RNA molecules that target an HCV nucleotide sequence selected from the group consisting of 3'-UTR, NS3 helicase, C1, C2, C3, C4, C5, 5B1, 5B2, 5B3, 5B4, 5B5, 5B6, 5B7, 5B8, 5U8, 5U9, 5U10, and the sequence targeted by siRNA5. Therefore, Kay cannot anticipate any of the rejected claims.

Accordingly, Applicants respectfully request withdrawal of the rejection of the various claims for allegedly being anticipated by Kay.

Rejections Under 35 U.S.C. § 103

On page 10 of the Office Action, claims 1-11, 14-40, 43, and 45-66 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kay in view of six cited references. A *prima facie* case of obviousness has three requirements. First, a single prior art reference or a combination of references must teach or suggest each and every claim feature of the claimed invention. *In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974). Second, there must be some reason, motivation, or suggestion to modify the single reference or combine the references in order to make the claimed invention. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Third, the prior art must provide "a reasonable expectation of success" that modifying the single reference or combining the references would result in the claimed invention. *Id.*

Applicants respectfully submit that the combination of Kay with any of the six cited references does not satisfy all three requirements for a prima facie case of obviousness against any of the pending claims. For example, Kay and the other cited references, either alone or in combination, do not teach RNA molecules that target an HCV nucleotide sequence selected from the group consisting of 3'-UTR, NS3 helicase, C1, C2, C3, C4, C5, 5B1, 5B2, 5B3, 5B4, 5B5, 5B6, 5B7, 5B8, 5U8, 5U9, 5U10, and the sequence targeted by siRNA5. Therefore, the combination of Kay with any of the cited references cannot render any of the claims obvious.

Accordingly, Applicants respectfully request withdrawal of the rejection of the various claims as allegedly being obvious over Kay in view of the cited references.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited. If there are any questions regarding the application, the Examiner is invited to contact the undersigned at the number below.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date November 22, 2006

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